A convenient synthesis of 2-benzoyl-1, 5-diphenylpyrroles, a class of potentially biologically active compounds

Asok K Mallik*, Surya K De & Falguni Chattopadhyay
Department of Chemistry, Jadavpur University, Kolkata 700 032, India
Email: mallikak52@yahoo.co.in

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Reaction of o-cinnamylideneacetophenones with nitrosobenzene in methylene chloride affords 2-benzoyl-1,5-diphenylpyrroles in very good yield through a [4+2]-cycloaddition of the reactants followed by a rearrangement of the cycloaddition product.

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A broad range of biological activity is associated with both simple and fused pyrroles and a large number of natural and synthetic compounds containing such moieties find pharmaceutical applications\(^1\). Thus, tolmetin and chlorpirac are two important synthetic pyrroles which structurally resemble the well-known anti-inflammatory agent indomethacin and the former is known to act as a prostaglandin synthetase inhibitor and finds use in rheumatoid arthritis. 2-Benzoyl-1,5-diphenylpyrroles having structural similarity with the said pyrroles, have been synthesised by us through a very simple reaction. Considering that 2 might have interesting biological activities, we report their synthesis in this paper.

Recently, synthesis of a type of potentially biologically active fused pyrroles, viz. 1,2-diphenyl-9H-[1]benzopyrano[3,2-b]pyrrole-9-ones 3, starting from \(o\)-hydroxy-o-cinnamylideneacetophenones 1 has been achieved by us\(^3\). Taking into account the possibility of formation of cycloaddition products from 1 and nitrosobenzene in neutral medium and facile rearrangement of such products to pyrrole derivatives\(^4\), we undertook a simple synthesis of 2-benzoyl-1,5-diphenylpyrroles 2.

Thus, on treatment of 2'-hydroxy-o-cinnamylideneacetophenone 1a with equimolar amount of nitrosobenzene in methylene chloride at room temperature, the bluish green colour of nitrosobenzene disappeared within 4 hr. The resulting material showing one major TLC spot yielded a pure compound after two crystallisations. In an alternative way, the same compound could be obtained in a somewhat greater amount by a quick filtration of the crude reaction mixture through a silica gel column. Characterisation of this compound from its analytical and spectral data showed that it was 2-(\(o\)-hydroxybenzoyl)-1,5-diphenylpyrrole 2a. Similarly, starting from other cinnamylideneacetophenones 1b-e, corresponding
pyrrole derivatives 2b-e were obtained in a very good yield. The above results indicate that the 3,6-dihydro-1,2-oxazines 4 formed by regioselective cycloaddition of 1 with nitrosobenzene are unstable and are transformed gradually to pyrroles 2. It may be mentioned here that unlike 6-methoxycarbonyl-3,6-dihydro-1,2-oxazoles 5 formed by cycloaddition of 1-methoxycarbonyl-4-arylbutadienes and nitrosobenzene, the 3,6-dihydro-1,2-oxazine 6 formed from [E,E]-hexa-2,4-dienal and nitrosobenzene is not isolable. The acidity of H-6 in the latter case has been made responsible for this difference. However, the product analogous to 3 was a minor product there, possibly due to control of reactivity of 6 and its ring opening product by the more reactive aldehyde group.

Experimental Section

All melting points are uncorrected. IR spectra were recorded in nujol on a Perkin-Elmer 297 Spectrophotometer, 1H NMR spectra in CDCl3 on Bruker DPX-300 (300 MHz), JEOL FX 100 (100 MHz). Bruker CXP-300 (300 MHz) spectrometers and mass spectrum on a JEOL D-300 spectrometer.

Reaction of α-cinnamylideneacetophenones with nitrosobenzenes

General procedure. To a stirred solution of α-cinnamylideneacetophenones (1, 1 mmole) in dry methylene chloride (20mL), nitrosobenzene (1 mmole) was added at room temperature and the reaction was allowed to continue until the blue colour of the dienophile disappeared (about 4 hr were required). Methylene chloride was then removed in vacuo and the residue was subjected to crystallisation column chromatography (over silica gel) in order to get the pure product. Yields, melting points, and analytical and spectral data of the pure products obtained thereby were as follows:

2a: Yield 78%; m.p. 118° (Found: C, 81.29; H, 5.06; N, 4.19, C23H17NO2 requires C, 81.41; H, 5.01; N, 4.13%); IR: 3420 (O-H) and 1640 cm⁻¹ (C=O); 1H NMR (100 MHz); δ 6.56 (1H, d, J = 4 Hz, H-4), 6.96-7.68 (13 H, m, Ar-H), 8.16 (1H, dd, J = 8 and 2 Hz, H-6") and 11.52 (1H, s, exchangeable with D2O, 2"-OH).

2b: Yield 84%; m.p. 160-61° (Found: C, 73.65; H, 4.42; N, 3.92. C23H16NO2Cl requires C, 73.89; H, 4.28; N, 3.75%); IR: 3430 and 1645 cm⁻¹; 1H NMR (300 MHz): δ 6.54 (1H, d, J = 4 Hz, H-4), 6.95 (1H, d, J = 9 Hz, H-3"), 7.02 (1H, d, J = 4Hz, H-3), 7.10-7.39 (10H, m, Ar-H), 7.42 (1H, dd, J = 9 and 2.6 Hz, H-4") and 8.04 (1H, d, J = 2.5 Hz, H-6") and 11.43 (1H, s, 2"-OH); MS: m/z 375 and 373 (M+, 14.1 and 39.9%), 307 (13.4), 281 (7.6), 219 (100), 180 (8.7), 115 (76), 89 (26.2), 77 (32.5) and 52 (27.5).

2c: Yield 77%; m.p. 163-64° (Found: C, 81.63; H, 4.99; N, 4.09. C23H16NO2 requires C, 81.58; H, 4.81; N,9.36%); IR: 3430 and 1650 cm⁻¹; 1H NMR (300 MHz): δ 2.36 (3H, s, CH3), 6.50 (1H, d, J = 4 Hz, H-4), 6.86 (1H, d, J = 8.6 Hz, H-3"), 6.97 (1H, d, J = 4 Hz, H-3), 7.09-7.36 (11H, m, Ar-H), 7.85 (1H, d, J = 1.7 Hz, H-6") and 11.35 (1H, s, 2"-OH).

2d: Yield 82%; m.p. 160-61° (Found: C, 78.30; H, 5.30; N, 3.86. C22H17NO3 requires C, 78.04; H, 5.15; N, 3.79%); IR: 3440 and 1645 cm⁻¹; 1H NMR (300 MHz): δ 3.82 (3H, s, OCH3), 6.48 (1H, d, J = 4 Hz, H-4), 6.92 (1H, d, J = 9 Hz, H-3"), 7.01 (1H, d, J = 4 Hz, H-3), 7.08-7.12 (3H, m, Ar-H), 7.18-7.25 (6H, m, Ar-H), 7.35 (1H, dd, J = 8.5 and 2.5 Hz, H-4") 7.56 (1H, d, J = 2.9 Hz, H-6") and 11.07 (1H, s, 2"-OH).

2e: Yields 90%, m.p.137° (Found: C, 85.61; H, 5.43; N, 4.47. C23H15NO requires C, 85.44; H, 5.26; N, 4.33%); IR: 1680 cm⁻¹; 1H NMR (300 MHz): δ 6.39 (1H, d, J = 4.2 Hz, H-4), 6.85 (1H, d, J = 4.1 Hz, H-3), 7.04-7.50 (13H, m, Ar-H) and 7.81 (2H, dd, J = 8.5 and 2.4 Hz, H-2",6").

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References